PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3585PTWO/AG/la		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/11642	21.10.2003	21.10.2002
International Patent Classification (IPC) or both national classification and IPC		
C07D487/22		
Applicant		
L. MOLTENI & C. DEI FRATELLI ALITTI SOCIETA DI...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 15 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.05.2004	21.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Boletti-Cremers, K Telephone No. +49 89 2399-8541

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11642

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 3, 4, 6-38	as originally filed
2, 2a, 5, 5a	received on 22.11.2004 with letter of 16.11.2004

Claims, Numbers

1-21	received on 22.11.2004 with letter of 16.11.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17,19-21

   because:

   ☒ the said international application, or the said claims Nos. 17,19-21 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16,18
	No:	Claims	

2. Citations and explanations

   see separate sheet

POINT III.

For the assessment of the presently worded claims 17 and 19-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a new medical treatment.

POINT V.

The following documents , quoted in the I.S.R., have been considered as relevant for the examination of the present application . Their numbering will be adhered to for the rest of the procedure.

(1) WO-A-01/96343, cited in the application.
(2) EP-A-0906 758, cited in the application .
(3) WO-A-02/10173, cited in the application.
(4) WO-A-98/33503.
(5) J.A.C.S. , 114(7), 2664-9, 1992.

1. Novelty.

1. The photosensitiser disclosed in (1)-(4) do not fall within the scope of present claims which can therefore be regarded as novel with respect to their contents.

2. The same conclusion can now be drawn from the content of (5) because the 2 single compounds disclosed in (5) , namely compounds 6 and 7 of (5), have been properly disclaimed from the claimed matter on file which can now be regarded as novel with respect to the content of (5).

2. Inventiveness

In view of the comparative argumentation submitted on 16.11.2004 by the Applicant , present

claims can be regarded as inventive with respect to the most relevant prior art (1) and (3). (5) is to be set aside because it relates to a quite different problem and according to the EP-regional practice , such a prior art can be avoided by means of a disclaimer (as on file).

It should be reminded that present claims have not been fully searched and that an additional search , focusing on the M and the respective R and R_1 definitions will be performed in the regional proceedings to come.

markedly limited efficiency and poor selectivity toward the eukaryotic cells and/or micro-organisms, and because of the prolonged persistence in the skin, which often may cause phenomena of generalised photosensitivity (Jori G., *J. Photochem. Photobiol., B: Biol.*, Vol. 36, pp. 87-93, 1996).

Thus it is evident how important it is to develop novel porphyrin compounds suitable for the use as therapeutic agents in PDT and as diagnostic agents, but not showing the limitations illustrated above.

Some substituted porphyrins and metalloporphyrins are disclosed in Dick D.L. et al. *J. Am. Chem. Soc.* 114 (1992) 2664-2669. Their encapsulation within the hydrophobic cavity of cyclodextrins is reported, providing inclusion complexes capable of mimicking the activities of heme-containing proteins.

Porphyrin derivatives bearing cationic groups have been previously described (Merchat et al. *J. Photochem. Photobiol.* 32, 153-157, 1996; Merchat et al. *J. Photochem. Photobiol.* 35, 149-157, 1996) and assessed for their photodynamic properties in the bacteria photoinactivation. These compounds bear trimethyl-anilinium groups or quaternary ammonium pyridinium groups in the meso-positions and therefore are endowed by a hydrophilic nature.

Other photosensitisers such as phthalocyanines having hydrophilic and/or amphiphilic characteristics are known; for example, the International Applications No. WO 01/96343 and WO 02/090361, and in the US Patent No. 5,965,598, all in the name of the Applicant, disclose various evenly substituted hydrophilic phthalocyanines, as well as non centrosymmetrical phthalocyanines bearing cationic or protonable group on the macrocycle.

Summary of the invention

The Applicant has now found a novel series of photosensitizers having particularly advantageous properties compared to the known compounds.

These novel compounds have shown optimum physical-chemical features for therapeutic applications, particularly in relation to their absorption in the region of the visible spectrum, high molar extinction coefficients, high quantum yield in singlet oxygen production, that is expressed by the photoinactivation of eukaryotic and prokaryotic cells.

The photosensitizers described by this invention are able to produce singlet oxygen by using various light sources and wavelengths. In particular they can be activated by visible red light radiation when the treatment of deep seated tumours on infections is required as well as by blue visible radiation or white light radiations when is preferable to treat by means of the photodynamic process more superficial

P is selected from the group consisting of O, CH_2, CO_2, NHCONH and CONH;
l is an integer comprised between 0 and 5;
W is selected from the group consisting of O, CO_2, CONH and NHCONH;
f is selected from between 0 and 1;
J is H or an alkyl group $(CH_2)_q$-CH_3, wherein q is an integer comprised between 0 and 20;
R_2 and R_3, equal or different from each other, are selected from between R and R_1, wherein R and R_1 are defined as above,
M is chosen from 2H and a metal selected from the group consisting of Zn, Mg, Pt, Pd, $Si(OR_7)_2$, $Ge(OR_7)_2$ and $AlOR_7$, wherein R_7 is chosen from between H and C1-C15 alkyl,
and pharmaceutically acceptable salts thereof,
with the exception of the following compounds:
a) compound of formula (I) wherein M is 2H, $R_1 = R_3 = H$, $R = R_2$ is a group of formula (II) in which s is 1, X is O, Y is $(CH_2)_3$, v is 1, Z is N, n = d = 1, m is 0, and $R_4 = R_5 = H$; and
b) compound of formula (I) wherein M is 2H, $R_1 = R_3 = H$, $R = R_2$ is a group of formula (II) in which s is 1, X is O, Y is $(CH_2)_3$, v is 1, Z is N, n = d = 1, m is 0, R_4 and R_5 form with Z a phthalimido group.

Further subject of the present invention are the processes for the preparation of the above said compounds of formula (I), the novel intermediates in these processes and the conjugates in which the compounds of formula (I) are site specifically conjugated with bio-organic carriers, such as aminoacids, polypeptides, proteins and polysaccharides.

The present compounds of formula (I), as well as the corresponding conjugates, are useful for the treatment of microbial infections (bacterial, fungal and viral), in the photodynamic treatment of tumour, pre-cancerous pathologies, and other hyperproliferative diseases.

The present compounds (I) and the corresponding conjugates are useful as well, as diagnostic agents for the identification of pathologically affected areas and for photodynamic sterilization of blood and blood derivatives.

Features and advantages of the present compounds of formula (I) will be illustrated in details in the following description.

Detailed description of the invention

By "saturated or unsaturated heterocycle possibly substituted" according to the invention, an heterocycle is preferably meant, which is selected from the group consisting of morpholine, piperidine, pyridine, pyrimidine, piperazine, pyrrolidine, pyrroline, imidazole, aniline and julolidine (2,3,6,7-tetrahydro-1H,5H pirido[3,2,1-*ij*] quinoline).